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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,308	02/26/2004	Thomas Jessel	5199-152	8009

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EXAMINER
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GAMETT, DANIEL C

ART UNIT	PAPER NUMBER
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1647

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/789,308	Applicant(s) JESSEL ET AL.	
	Examiner Daniel C. Gamett, PhD	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 21 February 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-80 is/are pending in the application.
- 4a) Of the above claim(s) 1-65 and 80 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 66-79 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/26/2004, 12/13/2006</u> | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. Applicant's election of Claims 66-79 and species SHh in the reply filed on 02/21/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Claims 1-65 and 80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 02/21/2007.
3. Applicants' assumption regarding the species election is correct. Identification of activators of Hh signaling recited in claim 76 was inadvertently omitted from the requirement. Claims 66-79 are under consideration insofar as they read upon methods comprising contacting cells with SHh.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claims 66-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
6. Claims 66 and 77 each recite in step (e), "the candidate modulator in step (b)". There is insufficient antecedent basis for this limitation as no candidate modulator is recited in step (b) of either claim.

Art Unit: 1647

7. Claims 66 and 77 are further unclear because they misdirect the skilled artisan. Step (e) recites comparing neural differentiation of cells in step (b), with neural differentiation of cells in step (c). The cells in step (b) have not been contacted with any known or candidate modulator, whereas the cells in step (c) have been contacted with both a candidate modulator and an activator of Hh signaling. Therefore, the recited comparison would not be informative. For purposes of further examination, the claims are interpreted as reciting a comparison between the cells in steps (c) and (d). Claims 67-76 are unclear as they depend from claim 66,

8. Claims 78 and 79 are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. The instant claims lack a correlation step. The claims do not recite a basis for making a correlation. Claim 78 has one category of treatment: a collection of cells contacted with a candidate modulator. In claim 79, said cells are *further* contacted in the presence of an activator of Hh signaling. This expression does not clearly indicate a second treatment group such that two collections of cells may be compared in the presence and absence of an activator of Hh signaling. It rather suggests sequential treatment, first with a candidate modulator, then with both modulator and activator.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 66-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a modulator neural differentiation and for identifying a modulator of an Hh signaling pathway wherein the activator of an Hh signaling pathway is an Hh protein, does not reasonably provide enablement for methods for identifying a modulator of an Hh signaling pathway wherein the activator of an Hh signaling pathway is anything other than an Hh protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claims 66-76 are drawn to methods for identifying a modulator of an Hh signaling pathway. Claims 78 and 79 are drawn to methods for identifying a modulator of Hh-dependent neural differentiation. The methods comprise incubating cells with an “activator of an Hh signaling pathway”. The specification provides at [0165-1666] a broad definition and non-limiting exemplary list for the term “activator of an Hh signaling pathway”. The list appropriately includes each of the known Hh proteins. The also list includes molecules which are not known to be directly involved with Hh signaling and for which any association with Hh signaling stems from common usage of intracellular pathways (e.g. calcium, PKC, PI3K) shared by many growth factors. The list therefore includes signaling molecules that are not specific to Hh signaling, some of which are identified in the specification. TGFβ, for

Art Unit: 1647

example, is identified as an activator of BMP, Hh, and FGF signaling [0156, 0166, 0180]. Wnt1 and Wnt2 are, of course, activators of Wnt signaling, but they are also identified as activators of Hh signaling [0166]. The specification provides no guidance as to how one could identify a modulator of an Hh signaling pathway if any of these molecules were used as the "activator of Hh signaling" in the claimed method. If, for example, Wnt1 were the "activator of Hh signaling", a test compound that gave a measurable result would be identified as a modulator of Wnt signaling or Wnt-dependent neural differentiation, but the result would not show that the test compound acts on a component of Wnt signaling shared with Hh. Further experimentation would be required to determine if the test compound actually modulates an Hh signaling pathway. The same can be said of any of the named growth factors and cytokines in [0166] and claim 76. The claimed method cannot identify a modulator of an Hh signaling pathway unless a known activator of an Hh signaling pathway is used. By encouraging the skilled artisan to employ molecules that are only coincidentally related to Hh signaling, the specification actually guides the skilled artisan away from identifying a modulator of an Hh signaling pathway.

11. Claim 77 is directed to a method of identifying a modulator of neural differentiation. The recited steps could achieve this goal because they do provide for a determination of neural differentiation. However, this claim, along with claims 66-76, 78 and 79, directs the artisan to contact cells with any one of a plethora of "activators". Many of the "activators" are intracellular molecules, such as p53, PI3 kinase, PKC, PLC, c-fos, cyclin D1, and etc. The specification does not provide for cells that do not intrinsically possess these molecules and so does not teach the skilled artisan how to controllably contact cells with these "activators". In addition to the multitude of named "activators", the list also includes "any analogue or homologue thereof".

Art Unit: 1647

The skilled artisan would be required to perform undue experimentation order to practice any of the methods of claims 66-79 with this indeterminably large genus of reagents.

*Claim Rejections - 35 USC § 103*

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 66-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5844079 (Ingham), issued December 1, 1998, in view of US Patent Application Publication 20020151056 (Sasai) filed May 16, 2001, US Patent Application Publication 20040092012 (Okano), filed October 3, 2001, and US Patent 6833269 (Carpenter), filed May 21, 2001. The instant claims are drawn to methods wherein collections of stem cells or neural progenitor cells are contacted with a candidate modulator in the presence or absence of an activator of Hh signaling and neural differentiation of the contacted cells is determined and compared. Ingham teaches (from column 42, line 52 to column 43, line 27) stem cells may be contacted with a hedgehog polypeptide to induce neuronal differentiation (including motor neurons) and to maintain the differentiated state. Ingham further teaches that such contacted cells can be used in assays for the identification of neurotrophic factors. Contacting stem cell with Hh would inherently result in the "repositioning" effect recited in instant claim 68-73 as this repositioning

Art Unit: 1647

is intrinsic to differentiation to motor neurons, which was taught by Ingham. By teaching the detection of neurotrophic factors as a use for cells differentiated by Hh, Ingham implicitly teaches an assay that includes treatment groups both with and without the factors and a determination of neural differentiation. Thus, Ingham teaches the concept of the instantly claimed methods. One of skill in the art would recognize that this concept could be generalized to a method for the discovery of compounds that modulate Hh signaling and/or neural differentiation. Ingham teaches several sources of stem cells or neural progenitors (column 45, line 43 to column 46, line 6), but Ingham does not expressly teach embryonic stem cells as recited in instant claims 67 and 72. Sasai teaches differentiation of embryonic stem cells into neural ectoderm by contacting cells with SHh [0195]. US Patent Application Publication 20040092012 (Okano) teaches differentiation of embryonic stem cells into motor neurons and GABAergic neurons by a process that includes contacting cells with SHh (see Abstract). Carpenter teaches (throughout) methods for making neural cells from human embryonic stem cells (see Abstract). The general protocol taught by Carpenter begins with contacting embryonic stem cells with SHh (see figure 2).

### *Conclusion*

14. No claims are allowed.



Art Unit: 1647

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG

Art Unit 1647

8 May 2007



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